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Non-imidazole Heterocyclic Histamine H₃ Receptor Antagonists

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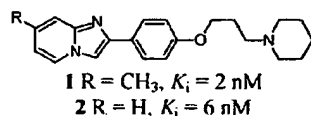
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Abstract—Continued exploration of the SAR around the lead imidazopyridine histamine H₃ antagonist **1** has led to the discovery of several related series of heterocyclic histamine H₃ antagonists. The synthesis and SAR of indolizine, indole and pyrazolopyridine based compounds are now described.

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Histamine receptors are divided into four subtypes, H₁,¹ H₂,² H₃,³ and H₄,⁴ at which histamine exhibits distinct pharmacological effects. Thus histamine plays a role in the pathogenesis of allergic conditions via the H₁ receptor and in gastric acid secretion via the H₂ receptor. H₁ and H₂ receptor antagonists have subsequently proven effective for the treatment of allergic diseases and gastric ulceration, respectively. The discovery of a third histamine receptor, H₃, by Arrang and co-workers,³ stimulated extensive research which demonstrated that the receptor is a presynaptic autoreceptor on histaminergic neurons and a presynaptic heteroreceptor on non-histamine containing neurons with greatest densities in the central nervous system.^{5–9} Consequently many applications have been proposed for H₃ receptor ligands, particularly in the CNS and centrally acting H₃ antagonists may provide novel therapies for neurological disorders such as epilepsy, sleeping disturbances, arousal/vigilance, ADHD and cognition.¹⁰



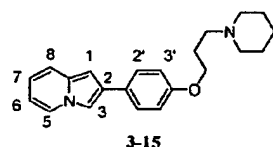
Earlier, we described¹¹ a series of imidazopyridines identified via high throughput screening, utilizing the

recombinant human H₃ receptor.¹² This afforded a potent and selective H₃ antagonist **1** with good oral bioavailability and blood–brain barrier penetration. Following this discovery we sought to explore replacements for the imidazopyridine nucleus which are the subject of this Letter.

Results

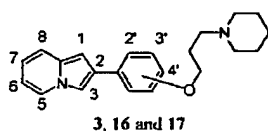
Throughout the study, we chose to retain the piperidinopropoxyphenyl fragment which is optimal according to our previous results.¹¹ This piperidinopropoxyphenyl fragment is also present in the potent non-imidazole H₃ antagonists described by other groups.^{13,14} Here, we only address replacements for the imidazopyridine nucleus together with substitutions in the heterocyclic and central phenyl rings. We first turned our attention to removing one of the heterocyclic ring nitrogens to afford indolizines and indoles. Thus the parent indolizine **3** (K_i = 13 nM) exhibited comparable activity to the corresponding imidazopyridine **2** (K_i = 6 nM) (Table 1). A range of simple substitutions were next examined. The attachment of a methyl group was tolerated with the five-membered ring, but with the six-membered ring, a reduction in affinity was observed. This contrasts with the results¹¹ for the imidazopyridine where analogous substitutions were favorable and suggests a slightly different receptor–ligand interaction for the indolizines. Although substitution in the phenyl ring led to reduced affinity (e.g., **14**), introduction of an additional substituent (e.g., **15**) to impart a steric

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Table 1. Indolizine and aryl ring substituents, oxypropylpiperidine terminus

| No. | Substituent | K_i (nM) |
|-----|--------------------------------------|--------------------|
| 3 | H | 13 (± 2.3) |
| 4 | 1-CH ₃ | 16 (± 2.6) |
| 5 | 3-CH ₃ | 2 (± 0.2) |
| 6 | 5-CH ₃ | 46 (± 13.1) |
| 7 | 6-CH ₃ | 28 (± 6.0) |
| 8 | 7-CH ₃ | 40 (± 7.4) |
| 9 | 8-CH ₃ | 40 (± 13.0) |
| 10 | 1-Ph | 40 (± 6.2) |
| 11 | 1-CH ₂ CH ₃ | 19 (± 2.1) |
| 12 | 3-CH ₂ CH ₃ | 5 (± 1.6) |
| 13 | 1-CH ₂ CH ₂ Ph | 37 (± 4.1) |
| 14 | 2'-CH ₃ | 152 (± 33.4) |
| 15 | 2',1-di-CH ₃ | 11 (± 3.2) |

K_i values for the human H₃ receptor were determined in house and calculated according to Cheng and Prusoff¹⁵ where $K_i = IC_{50}/(1 + [S]/K_d)$ where $[S] = 0.8$ nM and $K_d = 0.8$ nM for [³H]-N-methylhistamine. Values are means of three to seven experiments, SEM is given in parentheses.

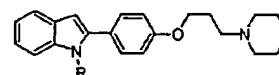
Table 2. Piperidinylpropoxy point of attachment

| No. | Substituent | K_i (nM) |
|-----|-------------|--------------------|
| 3 | 4' | 13 (± 2.3) |
| 16 | 3' | 308 (± 34.1) |
| 17 | 2' | 236 (± 89.9) |

interaction between the indolizine and the phenyl ring restored affinity. In the cases where a small substituent was tolerated, larger substituents were examined (e.g., 10–13) and found to be acceptable. However, no improvement in potency was observed. The point of attachment for the piperidinylpropoxy side chain was also examined (Table 2) and a decrease in affinity was observed as the point of attachment was moved from

Table 3. Heterocycle variations

| No. | R | K_i (nM) | No. | R | K_i (nM) |
|-----|---|------------------|-----|---|------------------|
| 2 | | 6 (± 0.1) | 18 | | 47 (± 6.4) |
| 3 | | 13 (± 2.3) | 20 | | 11 (± 1.2) |



18, R = H, $K_i = 47$ (± 6.4) nM
 19, R = SO₂CH₃, $K_i = 16$ (± 5.9) nM

Figure 1.

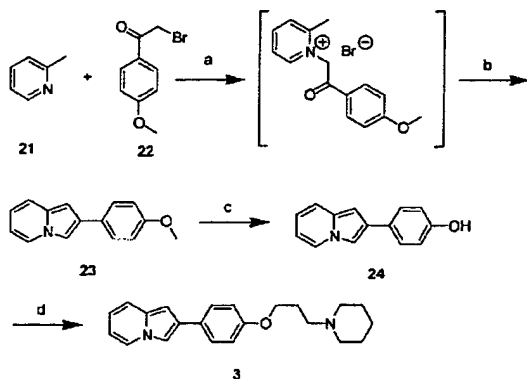
para to *meta* or *ortho*. We next prepared the indole analogue 18 recognizing that the indole nucleus contains a more acidic nitrogen than either the imidazopyridine or the indolizine nucleus (the calculated proton affinities of these heterocycles are in ref 16). In this case, a significant reduction in affinity was observed, although the sulfonamide intermediate 19 exhibited high affinity (Fig. 1).

One additional heterocyclic system was also examined, the pyrazolopyridine 20. In this case, the pyrazolopyridine system exhibited similar affinity to that observed for the imidazopyridine and indolizine system. The potencies for the different heterocycles shown in Table 3 apparently reflect the basicities of the heterocycles and a good correlation between their calculated proton affinities and their binding affinities was observed.¹⁶

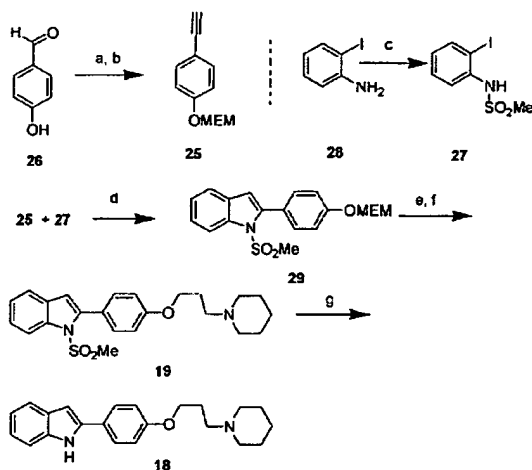
Synthesis

Syntheses of indolizine compounds (3–17) were accomplished according to the procedure outlined in Scheme 1 for the preparation of 3. 2-Picoline (21) was treated with α -bromoacetophenone (22) providing the 2-phenyl indolizine core 23. Demethylation of 23 gave 24 which was condensed with 3-chloropropylpiperidine affording 3.

The indole 19 was prepared according to Scheme 2. Phenylacetylene 25 was prepared from benzaldehyde 26 via initial protection of the phenol followed by acetylene formation¹⁷ using the Seyferth/Gilbert reagent.¹⁸ 2-Iodo-N-(methanesulfonyl)aniline 27 was obtained upon treating 2-iodo-aniline 28 with methanesulfonylchloride. Palladium mediated coupling reaction¹⁹ of 27 with 25 afforded the appropriately substituted indole core 29. Removal of the MEM (2-methoxyethoxymethyl) protecting group and alkylation of the free phenol under Mitsunobu conditions²⁰ gave protected indole 19 which was converted to 18.



Scheme 1. Regents and conditions: (a) acetone, reflux, 1 h; (b) K_2CO_3/H_2O , 5 h, 99% (a and b two steps); (c) $NaSEt/DMF$, 100°C; or $HBr/HOAc$, 100°C, 1 h; (d) $NaOtBu/DMF$, 3-chloropropylpiperidine, 100°C, 16 h, 93 or 90% (c and d two steps).

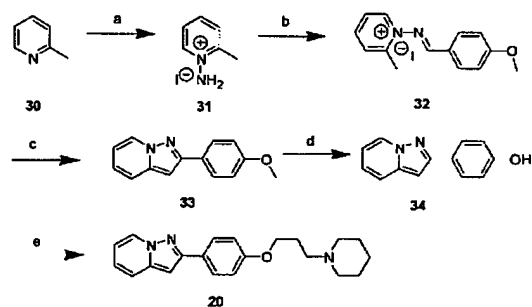


Scheme 2. Regents and conditions: (a) NaH , DMF , 1 h, rt; $MEMCl$, 16 h, rt, 87%; (b) $(MeO)_2POC(N_2)COMe$, K_2CO_3 , $MeOH$, 18 h, rt, 82%; (c) $MeCl$ (2 equiv), TEA , CH_2Cl_2 , 2 h, 0°C; KOH , 1:1 $MeOH/H_2O$, 1 h, rt, 74%; (d) $Pd(PPh_3)_4Cl_2$, CuI , 4:1 DMF/TEA , 18 h, 80°C, 89%; (e) 2N HCl , dioxane/ $MeOH$, 1 h, rt, 81%; (f) $DEAD$, polymer-supported PPh_3 , 3-hydroxypropylpiperidine, THF , 5 h, rt, 47%; (g) KOH , 1:1:1 $THF/MeOH/H_2O$, 12 h, rt, 20%.

Synthesis of pyrazolo[1,5-*a*]pyridine 20 was accomplished as shown in Scheme 3 using a published procedure²¹ for the key ring construction sequence (30–33). Picoline 30 was aminated to 31. Condensation of 31 with 4-methoxybenzaldehyde gave 32. Cyclisation of 32 then provided 2-phenyl-pyrazolo[1,5-*a*]pyridine 33. Demethylation of 33 gave 34 which was alkylated with 3-chloropropylpiperidine to afford 20.

Biological Results and Discussion

The indolizines, exemplified by 3, show comparable activity to imidazopyridine 2. However the corresponding indole 18 is less potent. The pyrazolopyridine 20 is moderately potent and overall receptor affinity appears



Scheme 3. Regents and conditions: (a) (i) HO_2SONH_2 , H_2O , reflux, 1 h; (ii) K_2CO_3 ; (iii) HI , 23%; (b) p -methoxybenzaldehyde, $MeOH$, reflux, 20 h; (c) I_2 , pyridine, 6 h, reflux, 10% (b and c two steps); (d) $HBr/HOAc$, 100°C, 3 h, 80%; (e) $NaOtBu/DMA$, 3-chloropropylpiperidine, 100°C, 16 h, 42%.

to be dictated by the basicity of the fused heterocycle. Indolizine 3 was examined in more detail and exhibited high selectivity with respect to a range of G-protein coupled receptors, ion-channels and transporters. (Inactive at concentrations below 500 nM). Its permeability (Caco-2) is high ($P_{app} = 14.1 \times 10^{-6} \text{ cm/s}$). In a functional assay versus the human H_3 receptor using SKNMC cells stably transfected with the human H_3 receptor 3 yielded a $pA_2 = 8.5$. The rat pA_2 was observed to be 7.71. In contrast to imidazopyridine 1, indolizidine 3 exhibited less binding to human serum albumin, 50% versus >90%, respectively. However whilst 3 showed a very favorable potency, selectivity and pharmacokinetic profile we were disappointed to observe rapid metabolism when 3 was exposed to human liver microsomes ($t_{1/2} \sim 10 \text{ min}$). Therefore we chose to examine additional compounds and found that the introduction of an alkyl group (e.g., 5) afforded a compound with superior stability ($t_{1/2} \sim 54 \text{ min}$) without loss of potency.

In conclusion, the imidazopyridine nucleus of 2 may be replaced by alternative fused heterocycles to afford potent histamine H_3 receptor antagonists that exhibit favorable properties for further development as therapeutic agents.

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16. The calculated proton affinities for **2**, **3**, **18**, and **20** are –242.09, –236.51, –220.08 and –228.89 kcal/mol, respectively. These data gave a good correlation with the measured K_i 's in Table 3 with an $R^2=0.827$. The sites of protonation for the heterocycles were N-1, C-3, C-3, and N-1 for compounds **2**, **3**, **18**, and **20**, respectively. The proton affinities were calculated at the B3LYP/cc-pVTZ(-f) + //B3LYP/6-31G** level of theory using Jaguar 4.1, Schrodinger Inc, Portland, OR, 1991–2000.
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